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Canadian Adverse Reaction Newsletter

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In this Issue

Oseltamivir and warfarin: increase in INR 1
Levonorgestrel-releasing intrauterine system and uterine perforation 2
Guidance document for industry 3
Energy drinks 3
Case presentation: Rosiglitazone: parotid gland enlargement 3
Summary of advisories 4

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Contact Health Canada or a Regional AR Centre free of charge
Phone: 866 234-2345
Fax: 866 678-6789

Form available at:
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Oseltamivir (Tamiflu) and warfarin: suspected increase in INR

Oseltamivir (Tamiflu), an antiviral drug marketed in Canada since 1999, is indicated for the treatment of acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days.[1] The drug is also indicated for the prevention of influenza illness in people over 13 years of age after close contact with an infected individual.

From Jan. 1, 1999, to Oct. 31, 2005, Health Canada received 19 reports of increased international normalized ratio (INR) suspected of being associated with the use of oseltamivir. These 19 reports involved patients aged 46 to 92 years (median age 84 years), and the indication for use of oseltamivir was either treatment or prophylaxis of influenza. All of the patients were taking warfarin. The reported onset of the adverse reaction ranged from the day treatment was started to 11 days after starting oseltamivir. The increased INR ranged from 3.2 to 10.9. Eleven of the reports were submitted by the same source and described a suspected interaction between oseltamivir and warfarin. Creatinine clearances were provided in these cases; dosage adjustments of oseltamivir were necessary in 3 cases, as recommended in patients with a creatinine clearance rate of 10–30 mL/min.[1] Six patients required treatment with vitamin K. At the time of reporting, 12 patients had recovered, 2 patients had not yet recovered, and the outcome was unknown for the remaining 5 patients.

Causality assessment of these cases is difficult because some of the reports presented conflicting or insufficient clinical information, and numerous factors (e.g., diet, medical conditions, fever) are known to influence a patient's response to anticoagulants.[2] In 3 cases, the warfarin dose was increased after the introduction of oseltamivir; the increases in INR occurred following these dose changes. In 3 other cases, decreases in INR occurred during the course of oseltamivir therapy without a reported change in warfarin dose. In 2 cases, clarithromycin and levofloxacin respectively were reported as co-suspect medications; these drugs are known to interact with warfarin and may cause increases in INR.[3,4]

Available data indicate that the potential for drug interactions with oseltamivir is minimal.[5] Oseltamivir requires conversion to the active metabolite via esterases, located predominately in the liver.[1] Drug interactions involving this pathway have not been commonly documented.[1,5] The drug does not

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interact with substrates of various cytochrome P450 isoenzymes.[5] Oseltamivir is not extensively protein bound and, as a result, is not expected to contribute to drug interactions involving protein-binding displacement. In addition, clinically important drug interactions involving competition for renal tubular secretion are unlikely.[1]

As with any drug prescribed to patients taking warfarin, more frequent monitoring of INRs may be prudent when oseltamivir is prescribed concurrently with warfarin. Health Canada continues to monitor adverse reactions suspected of being associated with the use of oseltamivir. Health care professionals are encouraged to report any cases of INR fluctuation in patients receiving warfarin and oseltamivir concomitantly.

Sally Pepper, BScPhm, Hima Murty, MDCM, CCFP, Health Canada

References

1. *Tamiflu (oseltamivir)* [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2004.
2. *Coumadin (warfarin)* [product monograph]. Montréal: Bristol-Myers Squibb Canada Inc.; 2002.
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5. Dutkowski R, Thakrar B, Froehlich E, et al. Safety and pharmacology of oseltamivir in clinical use. *Drug Safety* 2003;26(11):787-801.

Levonorgestrel-releasing intrauterine system (Mirena) and uterine perforation

The levonorgestrel-releasing system Mirena, an intrauterine device (IUD), consists of a polyethylene T-shaped frame with a reservoir containing levonorgestrel.[1] Mirena is indicated for use as a contraceptive and, after insertion into the uterus, continuously releases levonorgestrel at a low daily dose for up to 5 years. Mirena's contraceptive action is due mainly to local progestogenic effects on the uterine cavity, including a strong antiproliferative effect on the endometrium and a thickening of the cervical mucus, which prevents the passage of sperm. Ovulation is inhibited in some women. As of Nov. 28, 2005, the product monograph (PM) states that perforation or penetration of the uterus or cervix may occur during insertion but that this is very rare (less than 1 in 10 000). It also states that postpartum insertions should be postponed until 6 weeks after delivery.

From Feb. 22, 2001 (the date of marketing in Canada), to Sept. 26, 2005, Health Canada received 26 reports of uterine perforation suspected of being associated with the use of Mirena. In 8 of the cases, Mirena was inserted between 6 weeks and 6 months post partum. A long-term prospective study of Mirena found a higher uterine perforation rate (0.9 per 1000 insertions) than that described in the PM.[2] With copper IUDs, the rate of uterine perforation has been 0.6–1.6 per 1000 insertions.[3,4] In addition, evidence suggests that women who have IUDs inserted in the first 6 months post partum are at increased risk of uterine perforation.[5] This elevated risk may be due to the soft consistency of the uterus and the underestimated variability in uterine size during the first 6 months post partum.

Uterine perforation is a rare but serious complication of IUD insertion that occurs or is initiated at the time of insertion.[3] Evidence indicates that the rate of uterine perforation is lower in cases where the health care professional inserting the IUD has performed at least 10 previous insertions.[4] Currently, there is a shortage of health care providers trained in IUD insertion; access to good knowledge, proper equipment and a mentor to demonstrate and supervise several insertions are prerequisites to providing this service.[3,6]

Health care professionals inserting the levonorgestrel-releasing intrauterine system are encouraged to take this information into account. Special care should be taken with postpartum insertion, since perforations of the uterus have been reported.[7]

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1. *Mirena (levonorgestrel-releasing intrauterine system)* [product monograph]. Lachine (QC): Berlex Canada Inc.; 2000.
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Guidance document for industry: issuance of health product safety communications

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In August 2004, a draft version of this document was released for stakeholder consultation. A total of 183 comments were submitted by stakeholders, including pharmaceutical companies, pharmaceutical associations and academic centres. The comments were related to technical issues, clarifications and other issues. The final version of the guidance document has been updated in light of these comments. The Marketed Health Products Directorate would like to thank all those who participated in the consultation.

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Safe use of energy drinks

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Case presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Rosiglitazone (Avandia): suspected association with parotid gland enlargement

Health Canada has received 5 reports of parotid enlargement suspected of being associated with the use of rosiglitazone (Avandia). The cases involved 1 man and 4 women (age range 53 to 72, age not specified in 1 case). Some reports indicated multiple concomitant medications and a complex medical history. Four of the cases involved bilateral parotid enlargement, and 1 had enlargement of the parotid gland to 5 times its normal size. In 1 of the cases, swelling of the submandibular glands occurred as well, and in another case, parotiditis was considered as a differential diagnosis. The reaction onset was reported in 4 of the cases and ranged from 6 to 11 months after the start of the rosiglitazone therapy. The reaction was reported as painless in 3 cases. Upon withdrawal of the rosiglitazone therapy, 1 case reported improvement in 1 week, and in another case, there was gradual resolution of the reaction over 4 months. The outcome was not stated in 2 reports, and in the remaining case, the patient had not yet recovered at the time of reporting.

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Date	Product	Subject and type
Nov 10	Instant thermometers	Potential safety risk — consumer information
Nov 9	Weight loss products	Warning not to use certain weight loss products from China — consumer information
Nov 5	GenTeal Artificial Tears	Warning not to use Lot 51436 of GenTeal Artificial Tears — consumer information
Oct 31 & 5	Implantable medical devices	Interactions: active implantable medical devices and systems and other medical devices — notice to hospitals — notice to hospitals (revision)
Oct 25	Liqiang 4	Warning not to take Liqiang 4 — consumer information
Oct 25	Baxter infusion pumps	Important safety information — notice to hospitals
Oct 19	Gamunex	Hemolytic reactions — Talecris Biotherapeutics Inc. (Bayer Inc., Canadian distributor and importer) — notice to hospitals and consumer information
Oct 14	Flomax	Intraoperative floppy iris syndrome — Boehringer Ingelheim (Canada) Ltd. — health professional communication
Oct 6	Cardiac defibrillators	Safety information: implantable cardiac defibrillators — St. Jude Medical Canada, Inc. — health professional communication
Oct 6 & Sept 29	Paxil	Possible increased risk of birth defects — GlaxoSmithKline Inc. — consumer information and health professional communication
Oct 4	Long-acting β_2 agonists	Safety information about a class of asthma drugs — consumer information
Sept 29 & 28	Strattera	Potential for behavioral and emotional changes, including risk of self-harm — Eli Lilly Canada Inc. — consumer information and health professional communication
Sept 28	Kohl products	Traditional kohl products contain lead — consumer information
Sept 22	Insignia and Nexus pacemakers	Safety information: implantable pacemakers — Guidant Canada Corporation — health professional communication
Sept 21	Nimotop	Inappropriate administration of Nimotop capsules — Bayer Inc. — notice to hospitals
Sept 21	Celebrex	Important safety information — Pfizer Canada Inc. — consumer information and health professional communication
Sept 19	Linvatec surgical handpieces	Important safety information — notice to hospitals
Sept 16	Blood glucose monitors	Important safety information — Abbott Diabetes Care — consumer information
Sept 16 & 13	Duragesic	Important safety information — consumer information and health professional communication
Sept 8	Metallic airway stents	Important safety information — notice to hospitals
Sept 8 & Aug 31	Thioridazine	Important safety information — consumer information and health professional communication
Sept 7	Oxeze Turbuhaler	Important safety information — AstraZeneca Canada Inc. — health professional communication
Sept 7	Foradil	Important safety information — Novartis Pharmaceuticals Canada Inc. — health professional communication
Sept 7	Serevent	Important safety information — GlaxoSmithKline Inc. — health professional communication
Aug 31	Adderall XR	Safety information and Report of the Adderall XR New Drug Committee — Shire BioChem Inc. — health professional communication
Aug 26	Iressa 250 mg tablets	Important safety information — AstraZeneca Canada Inc. — consumer information and health professional communication
Aug 24	Adderall XR	Health Canada allows Adderall XR back on the Canadian market — consumer information

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MedEffect e-Notice

MedEffect e-Notice is the new name that replaces Health Canada's Health_Prod_Info mailing list. Subscribers will continue to receive notices of new safety advisories on health products along with the *Canadian Adverse Reaction Newsletter*. Thus, the content of the e-notices will remain the same and are now part of MedEffect, a new Health Canada Web site dedicated to adverse reaction information and reporting. MedEffect can be visited at: **www.healthcanada.gc.ca/medeffect**

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Suggestions?
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In this Issue

Tenofovir and NSAIDs: acute renal failure 1
Adverse reaction reporting — 2005 2
Isotretinoin: myocardial infarction, cerebrovascular and thromboembolic disorders 3
Case presentation: Overnight orthokeratology and *Acanthamoeba* keratitis 4
Summary of advisories 4
Regional Adverse Reaction Centres: relocation 6

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Tenofovir (Viread) and NSAIDs: acute renal failure

Tenofovir disoproxil fumarate (Viread) is an antiretroviral indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients 18 years of age and older.[1] Tenofovir was approved for use in Canada on Mar. 18, 2003, and was marketed on Mar. 15, 2004. Nephrotoxicity, including renal failure, renal insufficiency, elevated creatinine level, hypophosphatemia and Fanconi syndrome, has been reported with the use of tenofovir in clinical practice, as indicated under warnings and precautions in the product monograph.[1]

From Mar. 18, 2003, to Dec. 1, 2005, Health Canada received 22 domestic reports of adverse reactions suspected of being associated with the use of tenofovir. Ten of these reports involved nephrotoxic reactions, 3 of which were observed when a nonsteroidal anti-inflammatory drug (NSAID) was added along with the antiretroviral therapy, which included tenofovir. A short description of these 3 cases follows:

Case 1: A 53-year-old man with a normal serum creatinine level took tenofovir for 29 months along with other medications. After taking indomethacin (100 mg rectally twice daily) for 5 days to treat polyarthralgias, he experienced rectal bleeding, vomiting, acute renal failure and acute tubular necrosis. The indomethacin and tenofovir were discontinued. The patient required dialysis for 2 months; he had not yet recovered at the time of reporting.

Case 2: A 48-year-old man with a history of hepatitis C, ascites and liver insufficiency took tenofovir for 7 months along with other medications before starting therapy with naproxen (375-mg tablets prescribed 3 times daily). After taking 90 tablets over 2 months, the patient was admitted to hospital with acute renal failure and acute tubular necrosis. He died 3 days later.

Case 3: A 49-year-old man took tenofovir for more than a year with other medications. After 2 months of valdecoxib therapy (20 mg/d) for osteoarthritis, acute renal failure and nephrotic syndrome occurred requiring hospital admission. The valdecoxib was discontinued, all other medications were withheld, and the reaction abated.

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion.[1] Renal toxicity

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Sept 7	Serevent	Important safety information — GlaxoSmithKline Inc. — health professional communication
Aug 31	Adderall XR	Safety information and Report of the Adderall XR New Drug Committee — Shire BioChem Inc. — health professional communication
Aug 26	Iressa 250 mg tablets	Important safety information — AstraZeneca Canada Inc. — consumer information and health professional communication
Aug 24	Adderall XR	Health Canada allows Adderall XR back on the Canadian market — consumer information

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MedEffect e-Notice

MedEffect e-Notice is the new name that replaces Health Canada's Health_Prod_Info mailing list. Subscribers will continue to receive notices of new safety advisories on health products along with the *Canadian Adverse Reaction Newsletter*. Thus, the content of the e-notices will remain the same and are now part of MedEffect, a new Health Canada Web site dedicated to adverse reaction information and reporting. MedEffect can be visited at: **www.healthcanada.gc.ca/medeffect**

Canadian Adverse Reaction Newsletter

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Suggestions?
Your comments are important to us. Let us know what you think by reaching us at mhpd_dpsc@hc-sc.gc.ca

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Aussi disponible en français

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Health Canada Santé Canada

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Canadian Adverse Reaction Newsletter

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www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/index_e.html

In this Issue

Tenofovir and NSAIDs: acute renal failure 1
Adverse reaction reporting — 2005 2
Isotretinoin: myocardial infarction, cerebrovascular and thromboembolic disorders 3
Case presentation: Overnight orthokeratology and *Acanthamoeba* keratitis 4
Summary of advisories 4
Regional Adverse Reaction Centres: relocation 6

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Contact Health Canada or a Regional AR Centre free of charge

Phone: 866 234-2345
Fax: 866 678-6789

Form available at:

www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/index_e.html

Tenofovir (Viread) and NSAIDs: acute renal failure

Tenofovir disoproxil fumarate (Viread) is an antiretroviral indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients 18 years of age and older.[1] Tenofovir was approved for use in Canada on Mar. 18, 2003, and was marketed on Mar. 15, 2004. Nephrotoxicity, including renal failure, renal insufficiency, elevated creatinine level, hypophosphatemia and Fanconi syndrome, has been reported with the use of tenofovir in clinical practice, as indicated under warnings and precautions in the product monograph.[1]

From Mar. 18, 2003, to Dec. 1, 2005, Health Canada received 22 domestic reports of adverse reactions suspected of being associated with the use of tenofovir. Ten of these reports involved nephrotoxic reactions, 3 of which were observed when a nonsteroidal anti-inflammatory drug (NSAID) was added along with the antiretroviral therapy, which included tenofovir. A short description of these 3 cases follows:

Case 1: A 53-year-old man with a normal serum creatinine level took tenofovir for 29 months along with other medications. After taking indomethacin (100 mg rectally twice daily) for 5 days to treat polyarthralgias, he experienced rectal bleeding, vomiting, acute renal failure and acute tubular necrosis. The indomethacin and tenofovir were discontinued. The patient required dialysis for 2 months; he had not yet recovered at the time of reporting.

Case 2: A 48-year-old man with a history of hepatitis C, ascites and liver insufficiency took tenofovir for 7 months along with other medications before starting therapy with naproxen (375-mg tablets prescribed 3 times daily). After taking 90 tablets over 2 months, the patient was admitted to hospital with acute renal failure and acute tubular necrosis. He died 3 days later.

Case 3: A 49-year-old man took tenofovir for more than a year with other medications. After 2 months of valdecoxib therapy (20 mg/d) for osteoarthritis, acute renal failure and nephrotic syndrome occurred requiring hospital admission. The valdecoxib was discontinued, all other medications were withheld, and the reaction abated.

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion.[1] Renal toxicity

Newsletter and Advisories by email

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occurs with the accumulation of tenofovir in the proximal tubule and appears to be concentration dependent.[2] Cases of renal failure with tenofovir have been reported in patients with no known risk factors.[1] However, published case reports of nephrotoxicity suggest that there may be specific risk factors for the few patients in whom tenofovir-related nephrotoxicity develops.[2] Risk factors may include pre-existing renal dysfunction, long duration of use, low body weight, concomitant use of drugs that may increase levels of tenofovir (e.g., ritonavir), and other drug interactions.[2-4] Long-standing HIV infection itself may lead to higher incidence of nephropathy.[2]

Concurrent use of a nephrotoxic agent should be avoided with tenofovir, and the dosing interval should be adjusted in patients with a baseline creatinine clearance of less than 50 mL/min.[1] NSAIDs are frequently used and are available over the counter. Since NSAIDs are potentially nephrotoxic, their use during tenofovir therapy may represent an additional risk for renal failure.

Marielle McMorran, BSc, BSc(Pharm)

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1. *Viread (tenofovir disoproxil fumarate tablets)* [product monograph]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2005.
2. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005;40:1559-85.
3. Perazella MA. Drug-induced nephropathy: an update. *Expert Opin Drug Saf* 2005;4(4):689-706.
4. Fine DM. Tenofovir nephrotoxicity — vigilance required [editorial]. *AIDS-Read* 2005;15(7):362-3.

Adverse reaction reporting — 2005

The statistics for adverse reaction (AR) reporting for 2005 are presented in a new format to provide additional details. Health Canada received reports of 10 410 new domestic cases of suspected ARs to health products (pharmaceuticals, biologics [e.g., fractionated blood products, and therapeutic and diagnostic vaccines], natural health products and radiopharmaceuticals) in 2005, which were derived from 15 001 reports. The initial report and all subsequent information received as follow-up reports are combined and considered to be one case. Domestic cases were reported for the most part by health professionals, either directly to Health Canada or indirectly through another source (Table 1). A further analysis of the total number of cases by reporter type (originator) is outlined in Table 2. In Canada, Market Authorization Holders (MAHs) of health products are required to submit to Health Canada all reports of serious domestic ARs within 15 days. In addition, MAHs are required to send within 15 days all reports of serious unexpected ARs that have occurred outside Canada (foreign ARs) for the products they sell in other countries as well as in Canada.

Of the domestic cases received, 7223 (69.4%) were classified as serious.

Table 1: Source of domestic cases* of adverse reactions (ARs) received by Health Canada in 2004 and 2005

	No. (%) of cases received			
Source	2004		2005	
Manufacturer	6 114	(59.7)	6 482	(62.3)
Regional AR centre	3 617	(35.3)	3 470	(33.3)
Other†	507	(5.0)	458	(4.4)
Total	10 238	(100.0)	10 410	(100.0)

*Cases result from the merge of initial, follow-up and duplicate reports.
†Includes, but not limited to, professional associations, nursing homes, hospitals, physicians, pharmacists, Health Canada regional inspectors, coroners, dentists and patients.

Table 2: Number of domestic AR cases* by type of reporter (originator) in 2004 and 2005

	No. (%) of cases			
Reporter	2004		2005	
Pharmacist	3 011	(29.4)	2 592	(24.9)
Physician	2 667	(26.2)	2 970	(28.5)
Health professional†	1 499	(14.6)	1 267	(12.2)
Consumer/ patient	1 928	(18.8)	2 304	(22.1)
Nurse	873	(8.5)	926	(8.9)
Other	260	(2.5)	351	(3.4)
Total	10 238	(100.0)	10 410	(100.0)

*Cases result from the merge of initial, follow-up and duplicate reports.
†Type not specified in report.

In the Food and Drugs Act and Regulations, a serious AR is defined as "a noxious and unintended response to a drug which occurs at any dose and requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death." A serious unexpected AR is defined as "a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug."

The reporting of domestic ARs in Canada has increased steadily over the past 7 years, with 1.7% more cases in 2005 than in 2004 (Fig. 1).

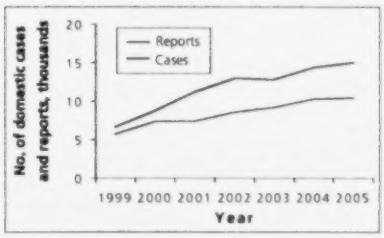

Fig. 1: Number of domestic reports and cases of adverse reactions (ARs) received by Health Canada from 1999 to 2005. (Reports include follow-up, duplicate and unenterable reports. Cases result from the merge of initial, follow-up and duplicate reports.)

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

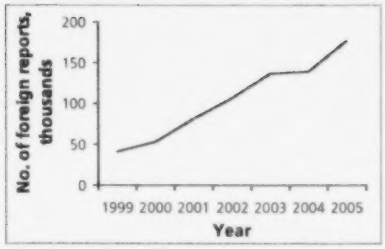

Fig. 2: Number of foreign AR reports received by Health Canada from 1999 to 2005. (Reports include follow-up, duplicate and unenterable reports.)

Health Canada also received 176 448 reports of foreign ARs in 2005, a greater than 4-fold increase since 1999 (Fig. 2). Because of this volume and the capacity of the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) database, foreign reports are not included in the domestic AR database.

Health Canada would like to thank all who have contributed to the program and encourages the continued support of postmarketing surveillance through AR reporting. ARs may be reported by using the toll free telephone (866 234-2345) and fax (866 678-6789) lines. Incidents involving medical devices are not collected in the CADRMP database and should be reported toll free through the Inspectorate Hot Line (800 267-9675).

Bill Wilson, BSc, BA, Health Canada

Isotretinoin (Accutane): myocardial infarction, cerebrovascular and thromboembolic disorders

Isotretinoin (Accutane) has been marketed in Canada since 1983 and is indicated for the treatment of severe nodular and inflammatory acne, acne conglobata and recalcitrant acne.[1]

From the date of marketing to Dec. 31, 2005, Health Canada received 29 domestic reports of vascular disorders or myocardial infarction suspected of being associated with the use of isotretinoin. Table 1 summarizes the 11 reports of stroke, thromboembolic disorders and myocardial infarction, all of which are not labelled adverse reactions (ARs) in the Canadian product monograph.[1] One report (case 8) provided laboratory test results for familial thrombophilias, lupus anticoagulant, anticardiolipin and anti-beta$_2$ glycoprotein antibodies, all of which were negative. Another report (case 10) indicated a positive result for lupus anticoagulant.

Health care professionals are encouraged to report any cases of myocardial infarction, cerebrovascular and thromboembolic disorders suspected of being associated with isotretinoin.

Pascale Springuel, BPharm, RAC; Gilbert Roy, BPharm, Health Canada

Table 1: Summary of reports submitted to Health Canada of myocardial infarction, cerebrovascular and thromboembolic disorders suspected of being associated with isotretinoin, from date marketed in Canada to Dec. 31, 2005*

Case	Reported reaction†	Age/Sex	Dose, mg‡	Time to onset§	Outcome¶	Risk factors or concomitant medical conditions
1	Myocardial infarction	25/M	80	4 mo**	Unknown	No known cardiac risk factors or family history
2	Stroke	18/M	60	2 mo	Recovered	None reported
3	Stroke	20/M	60	4 d	Recovered	Headache with visual disturbances, smoker. History of Raynaud syndrome, scleroderma, asthma, aphthae
4	Stroke	26/F	–	2 mo	Recovered	Hypertension
5	Cerebrovascular disorder	28/F	40	3 wk	Recovered	History of migraine
6	Cerebrovascular disorder	29/F	70	2 mo	Recovered	Hypertension, migraine, hypoglycemia with blackouts, cerebral hemorrhage (4 yr earlier)
7	Pulmonary embolism	20/F	50	3 mo	Recovered	Oral contraceptives
8	Pulmonary embolism	26/F	40	2 wk	Recovered	Obesity, hypertension, history of pulmonary embolism with isotretinoin + oral contraceptives 2.5 yr earlier
9	Thrombophlebitis	37/F	40	53 d	Recovered with sequelae	None reported
10	Hepatic vein thrombosis	15/M	40	Unknown	Not yet recovered	Diabetic, hypertension, antiphospholipid syndrome
11	Thrombosis	48/F	40	4 mo††	Unknown	None reported

***These data cannot be used to determine the incidence of adverse reactions (ARs) because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
†According to the *World Health Organization Adverse Reaction Terminology* (WHOART).
‡Average daily dose taken at the time of the AR, as indicated by the reporter.
§Estimated from the beginning of the treatment.
¶At the time of reporting, as indicated by the reporter.
**Within 5 weeks after a dose increase from 40 to 80 mg.
††Approximately 2 months following isotretinoin discontinuation.

Reference

1. *Accutane (isotretinoin)* [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2005.

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Case presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Acanthamoeba keratitis and overnight orthokeratology

In Canada, contact lenses are regulated as medical devices. Health Canada received a report of *Acanthamoeba* keratitis suspected of being associated with contact lenses worn for the purpose of orthokeratology (OK). OK is defined as the transient reduction in myopia through the use of a series of increasingly flat, reverse geometry, rigid, gas-permeable contact lenses that temporarily reduce the central curvature of the cornea.[1] Patients wear the contact lenses overnight.[1]

A myopic 12-year-old boy was fitted with Boston XO contact lenses for overnight OK. About 18 months later, he reported a sore right eye to the optometrist. After 1 week of treatment with an antiviral agent, the patient was seen by a local ophthalmologist for further care. Microbiologic testing identified *Acanthamoeba* species in cultures from both corneal scrapings and the contact lens. The patient reported following the office-recommended lens cleaning and disinfecting protocol with the commercially available solutions. At the time of reporting, the patient had not yet recovered.

Protozoan infections from *Acanthamoeba* are severe but rare in conventional use of rigid contact lenses and have been linked to contamination from water sources.[2] Published reports of acanthamebic keratitis in OK patients indicate that corneal scarring caused by these infections may necessitate corneal transplantation in affected patients.[1,3] Health Canada encourages health care professionals to report this sight-threatening complication of OK[1] that affects mostly teenagers,[3] as well as other adverse incidents involving contact lenses or other medical devices to the Health Products and Food Branch Inspectorate through the toll free hot line (800 267-9675).

References

1. Yepes N, Lee SB, Hill V, et al. Infectious keratitis after overnight orthokeratology in Canada. *Cornea* 2005; 24(7):857-60.
2. Watt K, Swarbrick HA. Microbial keratitis in overnight orthokeratology: review of the first 50 cases. *Eye Contact Lens* 2005;31(5):201-8.
3. Wilhelmus KR. Acanthamoeba keratitis during orthokeratology. *Cornea* 2005;24(7):864-6.

Summary of health professional and consumer advisories posted from Nov. 16, 2005, to Feb. 17, 2006
(advisories are available at www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html)

Date	Product	Subject and type
Feb 16 & Dec 19	Tequin	Serious hypoglycemia and hyperglycemia — consumer information — consumer information and health professional communication — Bristol-Myers Squibb Canada
Feb 9	Chinese herbal products	Potential health risks — consumer information
Feb 7	Ketek	Liver failure — consumer information
Feb 6	Methyl-1-testosterone	Warning not to use methyl-1-testosterone — consumer information
Feb 1	White Peony	Warning not to use White Peony scar-repairing pills — consumer information
Jan 31 & 12	Blood lancing devices	Transmission of blood-borne diseases — consumer information and notice to hospitals
Jan 26	Octreotide Acetate Omega	Recall of Octreotide Acetate Omega 500 µg/mL — consumer information and health professional communication
Jan 26	Libidfit	Warning not to use Libidfit — consumer information
Jan 24	WinRho SDF	Intravascular hemolysis — Cangene Corporation — consumer information and notice to hospitals
Jan 21	Pacemakers	Important safety information — Guidant Canada Corporation — health professional communication
Jan 19	M2 Formula and Energy 2000	Warning not to use M2 Formula and Energy 2000 — consumer information

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1. Yepes N, Lee SB, Hill V, et al. Infectious keratitis after overnight orthokeratology in Canada. *Cornea* 2005; 24(7):857-60.
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Summary of advisories continued from previous page

Date	Product	Subject and type
Jan 13	Enbrel, Humira and Remicade	Hepatitis B virus (HBV) reactivation — Amgen Canada, Inc., Abbott Laboratories, Ltd. and Schering Canada, Inc. — consumer information and health professional communication
Jan 12	Macugen	Hypersensitivity reactions — Pfizer Canada Inc. — consumer information and health professional communication
Jan	Blood Glucose Monitors	Important safety information — Becton Dickinson and Company — consumer information
Dec 28	Medical telemetry systems	Risk of electromagnetic interference — notice to hospitals
Dec 28	Linvatec surgical handpieces	Important safety information — notice to hospitals
Dec 28	Kaizen Ephedrine HCL	Advisory not to use Kaizen Ephedrine HCL tablets — consumer information
Dec 23	Tamiflu	Advisory to be cautious when buying Tamiflu online — consumer information
Dec 22 & 16	Paxil	Increased risk of cardiac defects following exposure during first trimester of pregnancy — GlaxoSmithKline Inc. — consumer information and health professional communication
Dec 21	Chaparral	Warning not to take products containing chaparral — consumer information
Dec 20 & 19	Avandia and Avandamet	New onset and/or worsening of macular edema — GlaxoSmithKline Inc. — consumer information and health professional communication
Dec 19	Implantable medical devices	Update: interactions — notice to hospitals
Dec 16	Bextra	Health Canada prohibits sale of Bextra in Canada — consumer information
Dec 15	Colleague pump	Important safety information — Baxter Corporation — health professional communication
Dec 7	Zevalin	Severe mucocutaneous reactions — Berlex Canada Inc. — consumer information and notice to hospitals
Dec 2	Pms-Sodium Phosphates oral solution	Kidney impairment and nephrocalcinosis — Pharmascience Inc. — consumer information and health professional communication
Dec 2	Fleet Phospho-Soda	Kidney impairment and nephrocalcinosis — Johnson & Johnson, Merck Consumer Pharmaceuticals — consumer information and health professional communication
Dec 2	Euro-ASA 80 mg	Warning to return bottles of Euro-ASA 80 mg chewable tablets — consumer information
Nov 30	Sigma series pacemakers	Important safety information — Medtronic of Canada Ltd. — health professional communication
Nov 28	Evra	Warning: clarification on status of Evra — consumer information
Nov 25	Aranesp	Pure red cell aplasia — Amgen Canada Inc. — consumer information and health professional communication
Nov 24 & 17	Femara	Contraindication in premenopausal women — Novartis Pharmaceuticals Canada Inc. — consumer information and health professional communication
Nov 23	Climacteron injection	Discontinuation of Climacteron injection — Sandoz Canada Inc. — health professional communication
Nov 21	Infusion pumps	Product recall: Baxter/Sabratek 6060 pumps — Baxter Corporation — health professional communication
Nov 18	GenTeal Gel	Warning not to use certain lots of GenTeal Gel — consumer information
Nov 18	Aquify comfort drops	Warning not to use certain lot of Aquify 2-ml long-lasting comfort drops — consumer information
Nov 17	Shortclean	Warning not to take the Chinese medicine Shortclean — consumer information
Nov 14 & 9	Accu-Chek Aviva	Safety information: Accu-Chek Aviva glucose monitors — Roche Diagnostics — consumer information and health professional communication

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Regional Adverse Reaction Centres: relocation

Health Canada announces the relocation of the Regional Adverse Reaction (AR) Centres in British Columbia, Saskatchewan, Ontario, Quebec and Atlantic Canada to the Regional Offices of the Health Products and Food Branch of Health Canada effective Apr. 1, 2006. The Regional AR Centres in Alberta and Manitoba were opened in April 2005 in Health Canada Regional Offices, and their location therefore will not change. The Regional AR Centres will be aligned with the Health Canada regions and will provide regional coverage for all provinces and territories.

To report a suspected AR to health products marketed in Canada, health professionals and consumers should telephone toll free (866 234-2345) or complete a copy of the AR Reporting Form and forward it to the appropriate Regional AR Centre or the National AR Centre by mail or by fax toll free (866 678-6789). Copies of the form are available from your Regional AR Centre or the National AR Centre, and the Canadian *Compendium of Pharmaceuticals and Specialties* (CPS).

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Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Regional Adverse Reaction Centres: relocation

Health Canada announces the relocation of the Regional Adverse Reaction (AR) Centres in British Columbia, Saskatchewan, Ontario, Quebec and Atlantic Canada to the Regional Offices of the Health Products and Food Branch of Health Canada effective Apr. 1, 2006. The Regional AR Centres in Alberta and Manitoba were opened in April 2005 in Health Canada Regional Offices, and their location therefore will not change. The Regional AR Centres will be aligned with the Health Canada regions and will provide regional coverage for all provinces and territories.

To report a suspected AR to health products marketed in Canada, health professionals and consumers should telephone toll free (866 234-2345) or complete a copy of the AR Reporting Form and forward it to the appropriate Regional AR Centre or the National AR Centre by mail or by fax toll free (866 678-6789). Copies of the form are available from your Regional AR Centre or the National AR Centre, and the Canadian *Compendium of Pharmaceuticals and Specialties* (CPS).

Canadian Adverse Reaction Monitoring — BC and Yukon
400–4595 Canada Way
Burnaby BC V5G 1J9
British_Columbia_AR@hc-sc.gc.ca

Canadian Adverse Reaction Monitoring — Alberta and Northwest Territories
Ste. 730, 9700 Jasper Ave.
Edmonton AB T5J 4C3
Alberta_AR@hc-sc.gc.ca

Canadian Adverse Reaction Monitoring — Saskatchewan
Rm. 412, 4th floor
101–22nd St. E
Saskatoon SK S7K 0E1
Saskatchewan_AR@hc-sc.gc.ca

Canadian Adverse Reaction Monitoring — Manitoba
510 Lagimodière Blvd.
Winnipeg MB R2J 3Y1
Manitoba_AR@hc-sc.gc.ca

Canadian Adverse Reaction Monitoring — Ontario and Nunavut
2301 Midland Ave.
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Canadian Adverse Reaction Monitoring — Québec
1001 Saint-Laurent St. W
Longueuil QC J4K 1C7
Quebec_AR@hc-sc.gc.ca

Canadian Adverse Reaction Monitoring — Atlantic
1505 Barrington St.
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Ste. 1625, 16th floor
Halifax NS B3J 3Y6
Atlantic_AR@hc-sc.gc.ca

National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9
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Canadian Adverse Reaction Newsletter

Marketed Health Products Directorate
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Ottawa ON K1A 0K9
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Fax 613 952-7738

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Suggestions?

Your comments are important to us. Let us know what you think by reaching us at mhpd_dpsc@hc-sc.gc.ca

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